IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

SUPPLEMENTAL EXPERT REPORT OF JEFF BOYD, PH.D.

Date: May 24, 2024

Jeff Boyd, Ph.D.

I. BACKGROUND AND QUALIFICATIONS

I am the director of the Institute of Cancer Research at the Feinstein Institutes for Medical Research, which is the research arm of Northwell Health (New York's largest healthcare provider). I also serve as the vice president, chief scientific officer and director of the Northwell Health Cancer Institute's Center for Genomic Medicine. In addition, I am a professor in the Department of Obstetrics and Gynecology and Department of Pathology and Laboratory Medicine at the Zucker School of Medicine at Hofstra/Northwell, where I hold an endowed chair as the Carol and Arnold Wolowitz Professor in Cancer Research. Concomitant with these positions, I was appointed as professor at the Cold Spring Harbor Laboratory in New York, with membership in the Cancer Genetics and Genomics Program of the NCI-designated Cold Spring Harbor Laboratory Cancer Center.

I received my bachelor's degree at Duke University and my master's and Ph.D. degrees in toxicology and biochemistry at North Carolina State University and completed my postdoctoral training in environmental pathology at the Lineberger Comprehensive Cancer Center of the University of North Carolina at Chapel Hill. Following that, I served on the faculty (as a section head of Gynecologic Pathobiology) of the National Institute of Environmental Health Sciences, National Institutes of Health. I then joined the University of Pennsylvania as an associate professor, Division of Gynecologic Oncology, within the Department of Obstetrics and Gynecology, with a joint appointment in the Department of Genetics. From 1997-2006, I worked at Memorial Sloan-Kettering Cancer Center in New York City, where I was director of the Gynecology and Breast Research Laboratory in the Department of Surgery, and director of the Diagnostic Molecular Genetics Laboratory in the Department of Medicine. While there, I was promoted to full member (professor) with tenure-of-title. I left Sloan-Kettering to become vice president of Oncology and Research and director of the Anderson Cancer Institute at the Memorial University Medical Center in Savannah, GA. I also held appointments as professor in the Departments of Obstetrics and Gynecology, Surgery, Medicine, and Division of Basic Medical Sciences, as well as assistant dean for Research at the Mercer University School of Medicine - Savannah. From 2008-2015, I was a tenured professor and held the Robert C. Young, MD, Chair in Cancer Research at Fox Chase Cancer Center in Philadelphia, where I also served as senior vice president, chief scientific officer, and chief of the Division of Molecular Pathology. In addition, I was founding director of the Cancer Genome Institute. From 2015-2020, immediately prior to taking my current position in New York, I was a professor (with tenure) and chair of the Department of Human and Molecular Genetics and professor of Obstetrics and Gynecology, as well as associate dean for Basic Research and Graduate Programs at the Herbert Wertheim College of Medicine at Florida International University in Miami. I also served as associate deputy director, Translational Research and Genomic Medicine, at the Miami Cancer Institute of Baptist Health South Florida. I was founding director of the Center for Genomic Medicine at the Miami Cancer Institute.

My research focuses on the genetics and molecular genetics of gynecologic and breast cancers. I have been supported by more than $25 million in grants from the National Institutes of Health ("NIH") or peer-reviewed NIH-equivalent grants and have served as principal investigator for a National Cancer Institute Specialized Program of Research Excellence (SPORE) grant in ovarian cancer. Additional awards include Distinguished Cancer Scholar from the Georgia Cancer Coalition (2006) and the Rosalind Franklin Award for Excellence in Ovarian Cancer Research

from the Ovarian Cancer National Alliance (2015). I have authored or coauthored more than 200 articles, reviews, book chapters and editorials on the molecular and genetic bases of gynecologic or breast cancers and have been invited to present more than 150 lectures on these topics throughout the world. I have served as a peer reviewer in many capacities, including as a standing member of scientific review groups of the NIH, the Department of Defense cancer research program, and the American Cancer Society, and as an editorial board member for seven scientific and clinical journals. I have also served as an ad hoc peer reviewer for approximately 45 scientific and clinical journals. Among my many committee and board memberships, I served as chair of the Scientific Advisory Committee for the Ovarian Cancer Research Fund (Alliance) for nine years and recently served a three-year term as an elected member of the Board of Directors for the Society of Gynecologic Oncology. My current research interests include the histogenesis (cell of origin) of ovarian carcinoma, the comprehensive genomic characterization of ovarian cancer stem cells, and the genomic basis of diethylstilbestrol ("DES")-induced carcinogenesis of the cervix and vagina of women exposed to DES in utero.

II. SCOPE OF REPORT

I was asked to review two posters authored by Dr. Ghassan Saed, as well as a study associated with those posters that he and his team published in 2023 (after it was rejected by several journals). I was also asked to opine on two studies involving murine macrophages and talcum powder led respectively by Dr. Angelo Mandarino in 2020 and Dr. Tania Emi in 2021. Finally, I was also asked to address the opinions of plaintiffs' expert Dr. Shawn Levy, which address, in part, genetics and ovarian cancer. All the opinions in this report are stated to a reasonable degree of scientific certainty. I am being compensated at the rate of $600 per hour for my work on this matter and $1,200 per hour for deposition and other testimony.

III. PLAINTIFFS' EXPERTS HAVE NOT SHOWN THAT THEIR PROPOSED MECHANISMS FOR OVARIAN CARCINOGENESIS ARE PLAUSIBLE

Plaintiffs' experts propose that talc causes inflammation, which leads to cancer, or that inflammation causes oxidative stress, which damages DNA, which results in cancer.[1] These explanations are simplistic, speculative and lack sufficient scientific support to be deemed plausible. All suffer from the same flaw to various degrees: they depend on large leaps of faith connecting one process to another.

A. Dr. Ghassan Saed and his research

In support of their opinions, many of plaintiffs' experts have cited to works by Dr. Saed and the underlying studies he conducted, which purportedly found that talc causes an oxidative stress

[1] *See* Second Am. Expert Rep. of Anne McTiernan, MD, Ph.D. ("2nd Am. McTiernan Rep.") at 81-86, Nov. 15, 2023; Second Am. Expert Rep. of Judith Wolf, MD ("2nd Am. Wolf Rep.") at 14-16, Jan. 12, 2024; Second Am. Expert Rep. of Laura M. Plunkett, Ph.D., DABT ("2nd Am. Plunkett Rep.") at 45-46, Nov. 15, 2023; Expert Rep. of Michele L. Cote, Ph.D., M.P.H. ("Cote Rep.") at 14-15, Nov. 15, 2023; Second Am. Expert Rep. of Rebecca Smith-Bindman, MD ("2nd Am. Smith-Bindman Rep.") at 10-11, Nov. 15, 2023; Am. Rule 26 Expert Report of Shawn Levy, PhD ("Am. Levy Rep.") at 15, Nov. 15, 2023.

response that is associated with an increased ovarian cancer risk, as well as "malignant transformation" of ovarian epithelial cells.[2]

Dr. Saed is an associate professor at Wayne State University who was retained by plaintiffs in talc litigation to opine on purported mechanisms by which the perineal use of talcum powder can contribute to the development of ovarian cancer. He sought to publish certain research related to the molecular effects of talc on cells in vitro in the peer-reviewed literature, including research originally developed for his MDL expert report. Dr. Saed's efforts at academic publication yielded only modest success; ultimately, he and his coauthors were able to publish two articles in lower-tier journals after the manuscripts were rejected by highly critical reviewers at higher impact journals.

The first paper, rejected from Gynecologic Oncology and ultimately published in Reproductive Sciences, was largely a repurposing of his MDL expert report (I refer to this as "Fletcher/Saed 2019" throughout this report). It purported to show certain "cellular effects of talc" in vitro including changes in an inflammatory biomarker, changes in cell proliferation, certain mutations known as single nucleotide polymorphisms (SNPs), and changes in redox enzyme levels. I discussed this article in depth in my original report (submitted herewith), and do not repeat that discussion here. The second published article was, in an earlier form, originally rejected by several respected journals. In a slightly revised form, it was finally accepted by an extremely obscure Italian journal called Minerva Obstetrics and Gynecology (I refer to this article as "Harper/Saed 2023"). That article purported to demonstrate increased levels of malignant transformation in talc-treated ovarian epithelial cells in vitro. In addition to the two published articles, Dr. Saed has also presented two posters containing abstracts related to the research underlying his second article at conferences. Because many of plaintiffs' experts continue to rely heavily on Dr. Saed's work, I discuss it at length. As set forth below, my critiques are similar to those addressed in the many negative peer reviews from journals that found Dr. Saed's studies too poorly executed and scientifically unsound to warrant publication.

Generally, the conclusions of Dr. Saed's studies are dependent upon multiple layers of speculation. These studies are replete with multiple flaws in study design, execution, and interpretation that completely undermine his stated conclusions. This is particularly evident in light of many of the results; for example, some of the cellular and genetic changes that Dr. Saed claims to have observed took place over such an extraordinarily rapid time period as to be grossly inconsistent with fundamental biological principles pertaining to the effects of any purported carcinogen.

Even if these findings were credible, the gap between Dr. Saed's research and his claim to have elucidated the origins of ovarian cancer in women exposed to perineal talc application is very large. At most, if his research had been conducted in a reliable manner, Dr. Saed's second paper would demonstrate that exposure of cell lines to talc in vitro can induce anchorage-independent growth. However, these observations have no bearing on whether ordinary use of talc in a woman's underwear (or perineal area) can cause ovarian cancer, which remains a speculative theory for which plaintiffs have offered no rational scientific support.

[2] *See* 2nd Am. McTiernan Rep. at 83; 2nd Am. Wolf Rep. at 15; Cote Rep. at 14; 2nd Am. Smith-Bindman Rep. at 10; Am. Levy Rep. at 12, 15.

B. Review of recent poster presentations by Ghassan M. Saed and coauthors

In 2020 and 2021, Dr. Saed and his coauthors presented posters in which they claimed to demonstrate malignant transformation of cells caused by exposure in vitro to talcum powder. These posters contained abstracts ultimately used in papers that were repeatedly rejected by reputable journals, and formed the basis for Harper/Saed 2023, the paper ultimately accepted and published in 2023 (online in 2021). Below, I explain some of the fundamental problems in the two abstracts/posters underlying Harper/Saed 2023.

1. Harper AK, Fan R, Majed R, King N, Morris RT, Saed GM. *Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts* (2020 abstract/poster)

This study purports to have found that talcum powder "induces malignant transformation of normal ovarian epithelial cells," which "represents a direct causation mechanism" through which perineal use of talcum powder causes ovarian cancer.[3] Despite this bold proclamation, the study does nothing of the sort.

As with Dr. Saed's prior research related to this issue, there are numerous serious methodological flaws in this study, and the study's conclusions are unsound and unsupported. I was not surprised to discover after I reviewed the 2020 abstract/poster that PLOS ONE peer reviewers who rejected this study variously described it as "written in such a manner that the science cannot be trusted"; requiring "major revisions"; reaching a "highly worrisome" conclusion about cell transformation "based on the results from unclear methodology"; and generally containing "critical fatal flaws" and "problems . . . too numerous to count."[4]

Initially, it is important to understand the context of how an abstract for this study came to appear in a supplemental edition of the journal Gynecologic Oncology. This abstract became publicly available online on March 28, 2020, when that journal released a supplement containing all of the abstracts that had been selected for presentation at the Society of Gynecologic Oncology (SGO) 2020 Annual Meeting on Women's Cancer, which was canceled due to the COVID-19 pandemic.[5] Dr. Saed's abstract, included in this supplement, had been selected to be a "Poster presentation" at the SGO's annual meeting. Illustrating the difference between acceptance as a poster for a

[3] Harper AK, Fan R, Majed R, King N, Morris RT, Saed GM. *Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts*. Gynecologic Oncology. 2020 Oct 1;159:140. I have additionally reviewed a copy of this abstract that appears substantively the same but was formatted to appear as a poster, as further explained below. I thus refer to these materials respectively as the "Harper/Saed 2020 abstract" and "Harper/Saed 2020 poster," and collectively as the "2020 abstract/poster." In addition, I have reviewed a manuscript of this study that Dr. Saed submitted to the journal Reproductive Sciences, which I refer to as the "2020 manuscript."

[4] SAED_SEPT222021_SUPPL_000128-146 (rejection and reviewer comments from Reproductive Sciences, including copy of submitted manuscript); SAED_SEPT222021_SUPPL_000100-104 (rejection and reviewer comments from PLOS ONE).

[5] *See* Huh, *51st Annual Meeting of the Society of Gynecologic Oncology*, Oct. 1, 2021, https://www.gynecologiconcology-online.net/article/S0090-8258(20)32327-1/fulltext.

convention and traditional peer review for publication, 842 abstracts were submitted to the SGO for its 2020 annual meeting, and 743 of them (88%) were accepted for presentation. Dr. Saed's abstract was not among the 49 that were selected to be given as "Scientific Plenary presentations," or even the 59 selected as "Featured Poster presentations."[6] Instead, it was among the remaining 635 abstracts merely presented as "Poster presentations."

The difference between poster review and peer review of publications is also evidenced in the fact that the manuscript corresponding to Dr. Saed's 2020 abstract/poster was repeatedly rejected when Dr. Saed submitted it to multiple journals for publication.[7] Most notably, Gynecologic Oncology itself rejected a manuscript Dr. Saed submitted in 2021 that reiterated the research, results and conclusions (nearly verbatim) of his 2020 study, while adding some additional testing, ostensibly to try to strengthen it.[8] It is thus virtually certain that Gynecologic Oncology would have rejected a manuscript solely addressing Dr. Saed's 2020 study as well.

Below, I explain some of the methodological flaws that are evident in each section of the 2020 Poster, which mirror the lack of adherence to accepted standards of professional scientific conduct displayed in Dr. Saed's previous work.

To place this study in context, the authors of this abstract/poster purport to present data extending work that Dr. Saed and some of the same coauthors previously published in Fletcher/Saed 2019.[9] In my previous expert report, I reviewed the manuscript for that 2019 study and explained in detail the extensive flaws in the study design, data interpretation, and conclusions of that paper,[10] as well as an accompanying lack of adherence to accepted standards of professional scientific conduct associated with laboratory data management and disclosures made in publication of the work.[11] The present study suffers from similarly egregious scientific flaws, weaknesses, and misrepresentations of data, as explained below.

Objective. This section incorrectly states that "[e]xposure to talcum powder was shown (in Fletcher *et al*. [2019]) to induce specific point mutations in key redox enzymes that altered their activities in both normal and epithelial ovarian cancer cells."[12] But the Fletcher/Saed 2019 study did not by any means demonstrate that cell mutations were induced by talcum powder, for all of

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6 *Id.*

7 *See* SAED_SEPT222021_SUPPL_000128-146 (rejection and reviewer comments from Reproductive Sciences, including copy of submitted manuscript); SAED_SEPT222021_SUPPL_000100-104 PLOS ONE Decision (rejection and reviewer comments from PLOS ONE).

8 *See* SAED_SEPT222021_SUPPL_000069-070. I discuss the additional analysis conducted for this 2021 manuscript in Section III.B.2 below.

9 Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM. *Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer.* Reproductive Sciences. 2019 Dec;26(12):1603-12 ("Fletcher/Saed 2019").

10 Expert Rep. of Jeff Boyd for General Causation *Daubert* Hr'g ("Boyd Rep.") at 4-19, Feb. 25, 2019.

11 *Id.* at 20-24.

12 Harper/Saed 2020 abstract (Objective); *see also* Fletcher/Saed 2019.

the reasons set forth in my original expert report.[13] For example, the authors of the 2019 study conflated changes in the ratios of pre-existing SNPs with mutations, presented ratios of one nucleotide to the other at various SNP sites in a qualitative rather than quantitative fashion, and failed to provide data on the activities of key redox enzymes, instead providing irrelevant data on changes in the levels of mRNA and protein associated with the genes encoding these enzymes. These and the other issues set forth in my prior report, which I incorporate herein, make Dr. Saed's current description of his 2019 study incorrect and misleading.

Methods. Dr. Saed states that he treated human normal ovarian epithelial cells and human primary peritoneal fibroblasts in vitro with a concentration of 100 or 500 µg/ml (micrograms per milliliter) of either talcum powder or the control substance TiO_2 (titanium dioxide).[14] The apparent purpose of this approach was to try to determine whether treatment with talcum powder induced changes that analogous exposures to the control substance did not. But essential information is missing from this description, including how many ml (or µl) were applied to the cells, how many cells were treated, and in what size tissue culture plate or petri dish the treatment took place. Thus, it is impossible to determine the dose of talcum powder (or control) that was used to treat an unknown number of cells, rendering the entire experiment uninterpretable from the perspective of cell dosing. These omissions are particularly troubling considering that Dr. Saed's 2019 study treated cells with very high, non-physiologic doses of talcum powder, making it untenable to extrapolate those experiments to perineal talcum powder application by women.[15]

Dr. Saed's peer reviewers raised similar concerns regarding Dr. Saed's methodology as described in his 2020 manuscript, questioning why the reported doses were chosen and their relevance to human exposure.[16] For example, one reviewer found "no justification for [Dr. Saed's] chosen dose range," questioning whether it was "a range that is expected in ovarian tissue with topical external application of talc powder" and at which dose "talc become[s] acutely toxic to ovarian cells."[17] Even Dr. Saed's coauthor Dr. Robert Morris asked, in an email to Dr. Saed and the other coauthors of the 2020 manuscript: "Are the concentrations [of talc] used physiologically possible (especially in the ovary)?"[18] Dr. Saed's 2020 abstract/poster and manuscript answer none of these questions, and I agree with all of the reviewers' criticisms of Dr. Saed's dose selection for the reasons stated above. I also agree with later peer reviewers that Dr. Saed's decision to use ovarian surface epithelial cells rather than fallopian tube cells significantly marginalizes his study given that scientists now agree that most high-grade serous ovarian cancers originate in the fallopian tubes.[19]

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[13] Boyd Rep. at 11-14.

[14] Harper/Saed 2020 abstract (Method).

[15] Boyd Rep. at 4-5.

[16] SAED_SEPT222021_SUPPL_000101-103; SAED_SEPT222021_SUPPL_000128.

[17] SAED_SEPT222021_SUPPL_000101; *see also* SAED_SEPT222021_SUPPL_000070 (Gynecologic Oncology reviewer of 2021 Saed manuscript (which incorporated the 2020 experiments) commenting that "the dose of talcum powder is extremely high," and "unlikely to ever replicate physiological dosing," which "is a major experimental flaw and makes interpretation of results very difficult").

[18] SAED_SEPT222021_SUPPL_000151.

[19] SAED_SEPT222021_SUPPL_000069-070 (Gynecologic Oncology reviewer later stating as to this experiment that "[t]he clinical relevance is questionable given the arbitrary dose selection of talcum powder, and *(cont'd)*

An additional issue with the methodology for Dr. Saed's 2020 study is that he employs a commercial cell transformation assay kit ("ab235698," manufactured by Abcam) to achieve a result that is both beyond the capabilities of that assay and biologically implausible. The ab235698 assay is intended to allow "measurement of cell transformation in mammalian adherent or suspension cells in response to stimuli that inhibit or induce transformation."[20] There is no indication anywhere that the assay, even if used correctly, is capable of showing or has been validated for the purpose of showing *malignant* transformation;[21] yet, that is what Dr. Saed purports to have used it to do.

In addition, the notion that a commercial cellular assay kit could be used to demonstrate malignant cell transformation after 72 hours of treatment with an agent is scientifically incoherent. Specifically, Dr. Saed states that his cells were treated with talcum powder or TiO_2 for 72 hours "before assessment with transformation assay," implying that a 72-hour exposure of normal ovarian epithelial cells to talcum powder is sufficient to convert them into fully malignant—i.e., cancerous—ovarian cells (given that the study purports to conclude that malignant transformation occurred).[22] That would not be possible in accordance with accepted principles of human cancer cell biology. For the process of malignant transformation to have occurred, mutations in multiple cancer-associated genes (specifically those found in ovarian carcinomas)[23] must have been induced and "fixed" through multiple rounds of cell division, in a majority of the cells. It would be biologically impossible for this to have occurred in a single 72-hour treatment. For these reasons, Dr. Saed's peer reviewers correctly found that his study failed to show malignant transformation and recommended that he excise that language from his manuscript.[24]

Results. This section of the 2020 abstract/poster begins by stating that "[a]nchorage-independent growth is a hallmark of cancer cells,"[25] a sentence that Dr. Saed appears to have nearly copied

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perhaps more importantly the examination of ovarian surface epithelial cells without comparison to fallopian tube secretory epithelium[,] [g]iven that the prevailing evidence suggests the origin of high-grade serous ovarian cancer is the fallopian tube"; later questioning why the authors did not address the fact that the fallopian tube fimbria is "the dominant site of origin for high-grade serous carcinoma," such that "it is conceptually difficult to understand why ascending talcum powder would preferentially affect the fimbria and not the more proximal portions of the FT").

[20] *See* Abcam, *ab235698 Cell Transformation Assay Kit (Colormetric)* ("ab2355698 Protocol Booklet") at 1, version 1b last updated Oct. 31, 2023, https://www.abcam.com/cell-transformation-assay-kit-colorimetric-ab235698.html.

[21] *See id.*

[22] Harper/Saed 2020 abstract (Method, Conclusion).

[23] *See* Cancer Genome Atlas Research Network. *Integrated genomic analyses of ovarian carcinoma*. Nature. 2011 Jun 6;474(7353):609 (reporting specific gene mutations associated with different ovarian cancer subtypes).

[24] SAED_SEPT222021_SUPPL_000101 (peer reviewer identifying the "use of a single *in vitro* soft agar assay to claim malignant transformation" as a "critical fatal flaw" in Dr. Saed's study and recommending that "[a]ll claims for 'malignant transformation' should be changed to 'cell transformation'"); *see also* SAED_SEPT222021_SUPPL_000069 (Gynecologic Oncology reviewer later finding that "the reliance on a single commercial assay for assessment of transformation that has not been established in the literature" was among "several major issues" with the 2020 experiments and "[o]f primary concern").

[25] Harper/Saed 2020 abstract (Results).

from the manufacturer of his assay kit without attribution and with one significant modification.[26] While it is correct that most human cancer cell lines are capable of proliferation in a semi-solid medium such as soft agar (as opposed to a solid, charged plastic surface as found in traditional cell culture plates or dishes), such anchorage-independent growth is not *per se* sufficient evidence of malignant transformation, as Dr. Saed's peer reviewers explained.[27] Indeed, well-accepted peer-reviewed research establishes that chronic proliferation (which itself is not established in Dr. Saed's study) is only one of the critical biological properties of malignant cells.[28] Of note, the manufacturer website from which Dr. Saed appears to have copied this sentence states that "[a]nchorage-independent cell growth is the hallmark of *cell transformation*," not "cancer cells," as stated in Dr. Saed's conspicuous alteration.[29] In short, Dr. Saed's conclusion that observing the formation of cell colonies demonstrates malignant transformation reflects a fundamental misunderstanding of cancer biology.

Dr. Saed further states that "[t]reatment with talcum powder resulted in formation of colonies, indicating cell malignant transformation in a dose-dependent manner."[30] None of this is correct either. For one thing, there is no indication of how colonies were counted (in any of the materials related to this study, including the laboratory notebook), as peer reviewers observed,[31] and it is therefore impossible to verify that colonies in fact formed in a dose-dependent manner. In any event, a dose-dependent response relationship cannot be ascertained with only two exposure doses.

Finally, the major quantitative conclusion of the 2020 study, that "[t]reatment with talcum powder significantly increased the number of transformed ovarian cells by 11% and 20% in the 100 and 500 µg/ml doses, respectively ($P < 0.05$)),"[32] is nonsensical. Above this statement, the authors had noted that "[t]here were ***no*** colonies formed in untreated ovarian cells or control ovarian cells at either dose."[33] Thus, the authors ultimately reported that colonies were increased by 11% and 20% of zero. It is a basic principle of elementary school math that any number multiplied by zero is

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[26] *See* https://www.abcam.com/cell-transformation-assay-kit-colorimetric-ab235698.html (stating under Product Overview: "Anchorage-independent cell growth is the hallmark of cell transformation."); ab2355698 Protocol Booklet at 3 (stating same); *see also* SAED_SEPT222021_SUPPL_000070 (reviewer identifying this among "[s]everal phrases . . . [that] appear to be taken verbatim from the manufacturers' websites").

[27] SAED_SEPT222021_SUPPL_000101 ("Soft agar colony formation alone in an in vitro test system is not enough data to claim malignant transformation."; "To show 'neoplastic transformation[,]'[] authors would need to conduct a more diverse battery of tests to show that these 'transformed' cells possess a tumor or cancer cell phenotype (i.e. cancer hallmarks), as outlined by Hannahan [sic] and Weinberg.").

[28] Hanahan, D, Weinberg RA. *Hallmarks of cancer: the next generation*. Cell. 2011 Mar 4;144(5):646-74. This article has been cited 35,424 times and carries a field-weighted citation impact of 257.92, according to the website www.scopus.com as of September 30, 2021.

[29] *See* https://www.abcam.com/cell-transformation-assay-kit-colorimetric-ab235698.html (emphasis added).

[30] Harper/Saed 2020 abstract (Results).

[31] SAED_SEPT222021_SUPPL_000104.

[32] Harper/Saed 2020 abstract (Results).

[33] *Id.* (emphasis added).

zero. A positive percentage in relation to the number zero is an arithmetical anomaly, to say the least, as was noted in peer review.[34]

Conclusion. The purported "conclusions" presented in Dr. Saed's 2020 abstract/poster and manuscript are incorrect, misleading, and unsupported by his data and methodology. First, the study did not show that "[e]xposure to talcum powder induces malignant transformation in normal ovarian epithelial cells" as claimed,[35] since the methodology employed was incapable of establishing malignant transformation, as explained above and as recognized by the peer reviewers.[36] This makes the title of Dr. Saed's 2020 abstract/poster and manuscript, which reiterates this conclusion, misleading in and of itself.

The 2020 abstract/poster and manuscript additionally conclude that the study's findings represent "a direct causation mechanism of talcum powder exposure specific to normal ovarian cells and further supports previous studies of the association of genital use of talcum powder and increased risk of ovarian cancer."[37] This egregious overstatement is not supported by the data presented in Dr. Saed's research, well-accepted scientific principles, or common sense. Even if the reported experiments and data had been interpretable and meaningful with respect to the hypothesis that exposing normal ovarian epithelial cells to talcum powder induces malignant transformation of the cells (based on a surrogate biological endpoint of anchorage-independent growth, which is itself an invalid endpoint for such a conclusion), this result would not "represent a direct causation mechanism" through which talcum powder exposure could cause ovarian cancer in women. Moreover, contrary to Dr. Saed's assertion, the overall body of epidemiological studies does not establish an increased risk of ovarian cancer from talcum powder use.[38] The cohort studies are most telling that there is no increased risk.[39] Such an increase would have been observed in epidemiology studies—and almost certainly would have been much larger—if Dr. Saed's research and conclusions were correct. As a reviewer explained, the claim that acute talc exposure leads to cell transformation after 72 hours "suggests that a single application of talc is extremely potent and carries high risk for cell transformation. Since talc powder is widely used, why aren't cancer rates much, much higher? . . . . Without adequate discussion or further data to support this claim, this finding is highly questionable."[40]

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[34] SAED_SEPT222021_SUPPL_000101-103 ("Page 5 states that the negative control was a blank. If so, how can you have a positive percent transformed cell response for this treatment?"); *see also* SAED_SEPT222021_SUPPL_000069 (Gynecologic Oncology reviewer later noting that "appropriate statistical tests were not applied and thus the data are difficult to interpret").

[35] Harper/Saed 2020 abstract (Conclusion).

[36] SAED_SEPT222021_SUPPL_000101-103.

[37] Harper/Saed 2020 abstract (Conclusion).

[38] *See, e.g.*, O'Brien KM, Tworoger SS, Harris HR, Anderson GL, Weinberg CR, Trabert B, Kaunitz AM, D'Aloisio AA, Sandler DP, Wentzensen N. *Association of powder use in the genital area with risk of ovarian cancer*. JAMA. 2020 Jan 7;323(1):49-59; Wentzensen N, O'Brien KM. *Talc, body powder, and ovarian cancer: a summary of the epidemiologic evidence*. Gynecologic Oncology. 2021 Oct 1;163(1):199-208.

[39] *See id.*

[40] SAED_SEPT222021_SUPPL_000101.

In summary, the essence of a direct causative mechanism for human carcinogenesis is neither implicit in, nor demonstrated by, the material presented in Dr. Saed's 2020 abstract/poster. Moreover, since the experiments conducted for Dr. Saed's 2020 study were incorporated into his 2021 study and its eventual publication, the issues described above apply with equal force to the studies discussed in the next two sections of this report, and to the published paper on which plaintiffs' experts rely in this litigation.

2. Saed GM, Harper AK, Morris R., *Talcum powder induces a malignant transformation in normal ovarian epithelial cells* (2021 poster)

Dr. Saed presented a second poster/abstract (LB-048) on July 8, 2021 at the 68th Annual Meeting of the Society for Reproductive Investigation (SRI), held in Boston, MA.

This poster reports on a 2021 study, which purports to supplement the 2020 study discussed above by incorporating those experiments and adding an "assessment of p53 and Ki-67 expression with immunohistochemistry (IHC)."[41] The new IHC analyses appear to have been conducted by the Wayne State University Department of Pathology rather than Dr. Saed or any of his coauthors, and it is unclear when these analyses took place or precisely how they were conducted.

Once again, I address the different sections of this abstract/poster in turn.

Background. The authors cite four publications that have purportedly "demonstrated an association between the genital use of talcum powder and an increased risk of ovarian cancer,"[42] but this is deceptive, and none of the four studies cited support the claim. The first cited study (Langseth 2008) concluded that current evidence is "insufficient to establish a causal association" and that "experimental research is needed . . . to evaluate the ovarian carcinogenicity of talc."[43] The second cited study (Henderson 1971) was not an epidemiology study or review and thus did not claim to describe an association between talc use and an increased ovarian cancer risk.[44] It instead reported pathological findings of talc particles embedded in ovarian and cervical tumors, concluding (contrary to Dr. Saed's basic theories) that "it is impossible to incriminate talc as a primary cause of carcinomatous changes within either the cervix or the ovary" based on those "preliminary observations."[45] The third cited study (Heller 1996) stated in its introduction that "[e]pidemiological evidence suggests that perineal exposure to talc is associated with an increased risk of epithelial ovarian cancer," but this was in 1996, before large cohort studies would seriously

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[41] Saed GM, Harper AK, Morris R. *Talcum powder induces a malignant transformation in normal ovarian epithelial cells* (2021 poster) ("Saed 2021 poster"). I have additionally reviewed a manuscript for this study that Dr. Saed submitted to Gynecologic Oncology on January 4, 2021, which I refer to as the "2021 manuscript."

[42] Saed 2021 poster (Background).

[43] Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. *Perineal use of talc and risk of ovarian cancer*. Journal of Epidemiology & Community Health. 2008 Apr 1;62(4):358-60.

[44] Henderson WJ, Joslin CA, Griffiths K, Turnbull AC. *Talc and carcinoma of the ovary and cervix*. BJOG: An International Journal of Obstetrics & Gynaecology. 1971 Mar;78(3):266-72.

[45] *Id.*

undermine that premise.[46] Moreover, Heller 1996 itself was a pathological rather than epidemiological study, and it drew into question the mechanistic theory that talc particles travel to the ovaries and cause cancer by finding that talc particle levels in normal ovaries were completely unrelated to reported levels of perineal exposure.[47] The fourth cited study (Muscat 2008) is a review article that also undermines Dr. Saed's theories, since it concluded that "[t]alc is not genotoxic"; that "[m]echanistic, pathology and animal model studies have not found evidence for a carcinogenic effect"; and that, ultimately, "these data collectively do not indicate that cosmetic talc causes ovarian cancer."[48]

Citing these same four studies, Dr. Saed and his coauthors proceed to state that "several in vitro studies have demonstrated a biologic effect when cells in culture are exposed to talcum powder."[49] This is a remarkable statement considering that none of those studies was an in vitro study, and none remotely suggests a biologic effect from treating cells in vitro with talcum powder. The authors then misrepresent Dr. Saed's previous work as supposedly having "delineated the molecular basis of the association of talcum powder use with increased risk of ovarian cancer."[50] This is a misrepresentation of that research, as discussed above and in my prior expert report. Finally, the authors state that "we have recently shown that exposure of normal ovarian epithelial cells to talcum powder induced transformation of these cells, using an agar transformation assay," apparently referring to the 2020 abstract/poster discussed above.[51] That claim, too, is deceptive and wrong, as explained in detail above.

Objective. The authors state that their aim was "to confirm that exposure of normal ovarian epithelial cells to talcum powder induces transformation of these cells with a different assay."[52] The use of the word "confirm" is misleading because no evidence of such transformation yet exists in the scientific literature.

Methods. The authors state that human primary ovarian epithelial cells ("HPOE") and ovarian epithelial cells ("HOSEpiC") were "treated with either 100 µg/ml of talcum powder or titanium dioxide (TiO_2) as a particulate control" before "assessment of p53 and Ki-67 expression with" IHC.[53] The first portion of this description appears to summarize the testing done in Dr. Saed's 2020 study, and likewise omits information (such as a description of the number of cells that were treated over a given surface area) needed to ascertain the talcum powder dosage for the experiments, rendering any results impossible to interpret. As to IHC analysis, it does not make scientific or logical sense to assert that IHC-demonstrated changes in expression of two proteins,

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[46] Heller DS, Westhoff C, Gordon RE, Katz N. *The relationship between perineal cosmetic talc usage and ovarian talc particle burden*. American Journal of Obstetrics and Gynecology. 1996 May 1;174(5):1507-10.

[47] *Id.*

[48] Muscat JE, Huncharek MS. *Perineal talc use and ovarian cancer: a critical review*. European Journal of Cancer Prevention. 2008 Apr 1;17(2):139-46.

[49] Saed 2021 poster (Background).

[50] *Id.*

[51] *Id.*

[52] *Id.* (Objective).

[53] *Id.* (Methods).

Ki-67 and p53, as documented by photographs, are evidence of conversion of normal cells to cancerous cells—issues that were echoed in peer review.[54]

Results. The results as described in the 2021 poster are unsupported by the data presented and methods used.

First, the authors imply that focal nuclear expression of the p53 protein, absent talcum powder treatment, indicates wild type p53 expression (which is jargon for the normal, non-mutated product of the *TP53* gene), while talcum powder treatment results in nuclear expression of "p53 mutated form."[55] This is nonsensical and scientifically unjustified. It has been well known for decades that nuclear expression of the p53 tumor suppressor protein, as assessed by IHC staining of cells, is a function of the half-life of the p53 protein. The half-life of p53 protein is typically quite short, and thus undetectable by IHC staining. In the presence of a myriad number of cellular states, the p53 protein may become stabilized to prevent cell division or activate programmed cell death (apoptosis), thus becoming detectable by IHC staining. While it is correct that p53 visualization may also reflect some types of *TP53* gene mutations, there are many *TP53* gene mutations that lead to absence of p53 expression. Until the authors have performed *TP53* gene sequencing in these cells (which is easily performed in any molecular biology laboratory), they have no basis to say there was evidence of *TP53* mutation, as was noted in peer review.[56]

Second, the authors state that "talcum powder treatment increased the proliferation index (PI) in both cell lines," from respective baselines of 50 and 70 percent to 90 percent, but do not describe the statistical analysis used to conclude that PI increased to 90 percent. The poster is silent on this, and the corresponding manuscript only says that PI "was assessed qualitatively using Ki-67-stained slides and classified as high PI (>50% positive cells) or low PI (<50% positive cells)."[57] It is unclear how a 90 percent PI increase was calculated based on these binary categories, as a peer reviewer explained.[58] And it is further not clear where the 90 percent result comes from, given that Dr. Saed's laboratory notebook never indicates a PI above 70 percent.[59] Regardless, increased cell proliferation does not demonstrate the malignant transformation of cells; there is no biological basis for drawing such a direct correlation.

In addition, the photographs presented in Figure 1 of the 2021 poster depict important inconsistencies that the authors fail to address.[60] Specifically, the effect of p53 stabilization is seen in a photograph of approximately 120 HPOE cells (third panel from left on top) but not in the photograph of HOSEpiC cells (sixth panel from left on top). Thus, there is an unexplained, dramatic discrepancy between the two ovarian cell lines with respect to talcum powder treatment

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54 *See* SAED_SEPT222021_SUPPL_000070 (reviewer explaining that "[t]he use of IHC to determine p53 mutation status is not very sensitive" and "needs to be confirmed with sequencing").

55 Saed 2021 poster (Results).

56 SAED_SEPT222021_SUPPL_000070.

57 SAED_SEPT222021_SUPPL_000079.

58 SAED_SEPT222021_SUPPL_000070.

59 *See* SAED_SEPT222021_SUPPL_000170-171.

60 Saed 2021 poster (Fig. 1).

and p53 expression. Additionally, the photographs suggest that the proportion of Ki-67 positive cells resulting from exposure to talcum powder and TiO_2 differed depending on the cell line at issue. In the HPOE cells (second panels from the left on top and bottom), there appears to be a higher proportion of Ki-67 positive cells in the cells treated with talc, while the proportion of Ki-67 positive cells in the HOSEpiC cells (fifth panels from left on top and bottom) appears to be at least as high or higher in the TiO_2-treated cells compared to the talc-treated cells. The authors do not address or attempt to explain these divergent results.

Finally, the captions to the photographs in Dr. Saed's laboratory notebook are inconsistent with what is stated in the 2021 poster and 2021 manuscript in several respects. First, the notebook captions state that the HOSEpiC cells treated with the *control* showed p53 mutation while the HOSEpiC cells treated with talc were consistent with "wild type" p53 and therefore *negative* for mutation.[61] The 2021 poster and 2021 manuscript state the opposite, however, i.e., that HOSEpiC cells treated with talc were positive for p53 mutation.[62] For Ki67, there is a similar issue, in that the notebook captions state that the HOSEpiC cells treated with the *control* showed "70% expression (high proliferation index)" while the HOSEpiC cells treated with talc showed "50% expression."[63] The statements in the notebook captions, if correct, would undermine Dr. Saed's theories since they indicate either no reaction or less of a reaction from talc. While it is possible that the caption statements in the notebook are errors, that would only further suggest poor laboratory practice.[64]

Conclusion. The conclusions stated in the 2021 poster and 2021 manuscript are materially the same as those of the 2020 abstract/poster: that "[e]xposure to talcum powder induces malignant transformation in ovarian epithelial cells" and that the authors' "findings represent a direct effect of talcum powder exposure and further support previous studies demonstrating a link between the genital use of talcum powder and increased risk of ovarian cancer."[65] These claims are misleading and devoid of scientific merit, for the reasons outlined above. Moreover, inasmuch as all of Dr. Saed's talc-related experiments have been performed with cells cultured in plastic petri dishes in vitro, the assertion of "a link between the genital use of talcum powder and increased risk of ovarian cancer" is even more misleading and unsupported.

For these reasons, I was not surprised to learn that Gynecologic Oncology rejected the manuscript Dr. Saed submitted for this study, with peer reviewers explaining that the study contained "several major issues," was of "questionable" "clinical relevance," and reflected data that were both "difficult to interpret" and "too premature for publication."[66] I am thus now aware of two rejections of Dr. Saed's manuscripts by this journal (the first being when he submitted the manuscript for

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61 SAED_SEPT222021_SUPPL_000171.

62 Saed 2021 poster; SAED_SEPT222021_SUPPL_000173.

63 SAED_SEPT222021_SUPPL_000171.

64 *See* Boyd Rep. at 20-23.

65 Saed 2021 poster (Conclusion).

66 SAED_SEPT222021_SUPPL_000069-070.

what became Fletcher/Saed 2019).[67] In addition, two other journals—Reproductive Sciences and PLOS ONE—rejected the manuscript corresponding to this 2021 poster. All of this is a strong signal that the scientific community thoroughly rejects Dr. Saed's methods and conclusions.

In summary, like the rest of his related research, the flawed additional testing that Dr. Saed and colleagues conducted in connection with their 2021 poster does not demonstrate a mechanism through which talcum powder can cause cancer in humans.

C. Harper AK, Wang X, Fan R, Mangu TK, Fletcher NM, Morris RT, Saed GM. *Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells*. Minerva Obstetrics and Gynecology. 2021 Nov 26;75(2):150-7

Dr. Saed's 2021 manuscript, with some alterations (as discussed below), was later accepted for publication and published by the Italian journal "Minerva Obstetrics and Gynecology,"[68] an English-language rebranding of the journal Minerva Ginecologica, a journal that is so obscure that it is the *101st ranked* Obstetrics and Gynecology journal by impact score on the website Scimago, which categorizes it as a second-tier ("Q2") journal.[69]

By contrast, Gynecologic Oncology, which rejected an earlier version of the manuscript Minerva Obstetrics and Gynecology published, and had previously rejected Dr. Saed's 2019 study, is the 12th ranked Obstetrics and Gynecology journal by impact score on Scimago.[70] Putting these rankings further into perspective, Minerva Obstetrics and Gynecology is the *3,942nd ranked* medical journal by impact score according to that website.[71]

In Harper/Saed 2023, Dr. Saed retreats from some of the bold and scientifically unjustified assertions he made in his 2020 abstract/poster and related manuscript, and his 2021 poster and manuscript. For example, Dr. Saed no longer asserts that "numerous epidemiological studies" establish a link between talcum powder use and ovarian cancer.[72] He instead now states: "The link between talcum powder exposure and ovarian cancer have [sic] been supported by the harmful biological effects reported in various cell culture studies."[73] I note that one of the sources Dr. Saed

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67 Sept. 19, 2018 email from Gynecologic Oncology to G. Saed re: GYN-18-2020: Final Decision.

68 Harper AK, Wang X, Fan R, Mangu TK, Fletcher NM, Morris RT, Saed GM. *Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells*. Minerva Obstetrics and Gynecology. 2021 Nov 26;75(2):150-7 ("Harper/Saed 2021").

69 *See* https://www.scimagojr.com/journalrank.php (sort "subject categories" to Obstetrics and Gynecology) (last visited Mar. 26, 2024).

70 *See id.* (same sorting).

71 *See id.* (sort "subject areas" to Medicine).

72 *Compare* Harper/Saed 2021 at 7, *with* SAED_SEPT222021_SUPPL_000084.

73 Harper/Saed 2021 at 7.

cites in support is his 2019 study, and a second is the 2007 study by Buz'Zard and Lau, which showed cell proliferation actually *decreased* with increased exposure to talc.[74]

Perhaps the most notable change reflected in Dr. Saed's 2023 publication is that Dr. Saed now states that "[a]nchorage-independent growth is one of the hallmarks of cell transformation," apparently attempting to correct his previous claim that such growth is a "hallmark of cancer cells."[75] I explained above why Dr. Saed's prior wording was misleading and scientifically unjustified above; in short, cell proliferation alone does not demonstrate malignant transformation. This is a scientific fact that virtually all of Dr. Saed's peer reviewers have emphasized. Unfortunately, these minor revisions fall far short of making Dr. Saed's methodology or conclusions scientifically reliable. And Dr. Saed continues to proclaim that the study found malignant transformations throughout the Harper/Saed 2023 paper.

As to methodology, nothing appears to have changed, meaning that the actual experiments underlying the 2023 publication were the 2020 cell culture experiments discussed in Section III.B.1 above, plus the additional IHC analysis added for the 2021 poster and manuscript, discussed in Section III.B.2 above. Having reviewed the 2023 publication, I see no indication at all that new or modified experiments were conducted. Illustrating this, while there are some (mostly structural) changes to the Discussion section of the 2023 publication, the Methodology section is essentially unchanged from what was stated in Dr. Saed's 2021 manuscript (rejected by Gynecologic Oncology and others), which as explained above, incorporated Dr. Saed's 2020 manuscript (rejected by Reproductive Sciences and PLOS ONE). All my criticisms of the methodology used for the posters above thus apply with equal force to what was done (or not done) for Dr. Saed's 2023 publication.

Given that there are no new experiments or methodological updates, it is perhaps unsurprising that Dr. Saed's conclusions remain essentially unchanged. He states, for example: "Here we clearly demonstrate that exposure to talcum powder induces malignant transformation in human primary normal ovarian epithelial cells and thus, providing a mechanism for the increased risk of ovarian cancer with the genital use of talcum powder."[76] For all of the reasons explained above, Dr. Saed's experiments establish neither malignant transformation nor a biological mechanism through which talcum powder use could cause ovarian cancer, and these conclusions remain just as scientifically baseless and inappropriate as before. Later, Dr. Saed reaches even further and concludes: "This study clearly demonstrate [sic] that talcum powder exposure induced malignant transformation of normal ovarian cells in culture which adds to the strong evidence of a causal relationship between

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[74] *See id.*; *see also* Buz'Zard AR, Lau BH. *Pycnogenol® reduces talc-induced neoplastic transformation in human ovarian cell cultures.* Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2007 Jun;21(6):579-86 ("Buz'Zard & Lau 2007").

[75] *Compare* Harper/Saed 2021 at 9, *with* SAED_SEPT222021_SUPPL_000080. Dr. Saed also no longer claims in his published study that that the signal generated by his cell transformation assay "can accurately determine number of transformed cells"—although it is possible that he only changed this language because a peer reviewer pointed out that he had copied it from the manufacturer's website. *Compare* Harper/Saed 2021 at 9, *with* SAED_SEPT222021_SUPPL_000081; *see also* SAED_SEPT222021_SUPPL_000070 (identifying that and other instances of copying).

[76] Harper/Saed 2021 at 3.

the genital use of talcum powder and ovarian cancer."[77] Again, the experiments discussed herein did not establish malignant transformation at all, much less "clearly." Further, as I and multiple peer-reviewers have explained, there is not and has never been "strong evidence" of a causal relationship between use of talcum powder and ovarian cancer.

In sum, Dr. Saed ultimately managed to have his 2023 study published in an obscure journal, but he did not make any changes to the deeply flawed methodology he used to generate the scientifically unreliable conclusions he offers regarding a purported biological mechanism for the alleged link between talcum powder use and ovarian cancer.

Despite the multiplicity of errors listed above, nearly all of plaintiffs' experts expressly rely on this study to claim that talcum powder causes malignant cell transformation. Dr. McTiernan concludes that this "recent study found that talcum powder induced malignant transformation in normal human primary ovarian epithelial cells, in a dose-dependent manner. (Harper, Wang et al. 2023)."[78] The same conclusion is listed in Dr. Smith-Bindman's latest report where she wrote "Harper and colleagues recently found that exposure to talcum powder induces malignant transformation in normal human ovarian cells (2023)."[79] Dr. Singh echoed them in writing, saying: "Harper . . . provided evidence that exposure to talcum powder induces malignant transformation in ovarian epithelial cells."[80] These are patently incorrect conclusions, perhaps because none of these experts are cellular biologists with experience conducting in vitro studies of this sort. Plaintiffs' experts' blind reliance on the statements written by Dr. Saed without any assessment of the study's techniques or methods is disturbing and further calls into question the biological plausibility opinions in these experts' reports.

D. Other Mechanistic Studies Relied Upon By Plaintiffs' Experts

In addition to the studies conducted by Dr. Saed that more directly attempted to evaluate carcinogenicity, plaintiffs' experts have begun relying on two studies examining the effects of talc on gene expression in certain rodent immune cells.[81] These studies do not attempt to demonstrate the effects of talc on normal human ovarian cells and are of minimal relevance to the biological plausibility questions raised in this litigation.

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77 *Id.* at 9-10.

78 2nd Am. McTiernan Rep. at 83.

79 2nd Am. Smith-Bindman Rep. at 14.

80 Suppl. Expert Rep. of Sonal Singh, MD, MPH at 13, Nov. 15, 2023.

81 *See* 2nd Am. McTiernan Rep. at 83; 2nd Am. Wolf Rep. at 15; 2nd Am. Plunkett Rep. 27 at 46-47; Cote Rep. at 14; 2nd Am. Smith-Bindman Rep. at 10.

1. Mandarino A, Gregory DJ, McGuire CC, Leblanc BW, Witt H, Rivera LM, Godleski JJ, Fedulov AV. *The effect of talc particles on phagocytes in co-culture with ovarian cancer cells*. Environmental Research. 2020 Jan 1;180:108676

This study explored the potential effects of talc and estrogen (E2) alone or in combination on mouse macrophage cell lines (a type of immune cell that can target and kill tumor cells) grown together with mouse "ovarian cancer" cells (ID8).[82] The authors' goal was to model the observation in some case-control studies that high estrogen might enhance the purported carcinogenic effects of talc. They claim that macrophage cell lines treated with both talc and estrogen increased reactive oxygen species (ROS) production, changed the expression levels of genes related to immune surveillance and cancer development, and decreased the tumoricidal effect of the macrophages compared to controls. The main problem with this study is that it has nothing to do with transformation (malignant or not) of normal ovarian cells. Beyond the critical relevance issue, this study suffered from numerous, fundamental flaws detailed below.

First, the choice of macrophage cells that were studied is questionable. Not only did the authors use murine cells (rodent), but they selected macrophagic-like cell lines as opposed to primary macrophages (those obtained directly from mice or humans), which further weakens the relevance of this study as it relates to human ovarian cells. Cell lines typically have acquired genetic and phenotypic differences and may be more unstable or atypical compared to primary macrophages derived from a patient directly.

Second, the dose of E2 used (2 µg/ml) is so high as to be clinically useless. A dose of 2 µg/ml translates to a concentration amount of 2,000,000 pg/ml, whereas normal blood levels of E2 in women are in the range of 30-400 pg/ml. Even crediting the possibility that levels of E2 are higher in the ovary area as compared to normal blood serum levels (around 4,000 pg/ml), the doses used in this study are too high to be physiologically relevant. Similarly, the relevance of the talc concentration chosen (10 µg/well) is unclear, as there is nothing correlating it in the study to the amount used in powder application to the perineum. As a side note, the authors used chemical grade talc from J.T. Baker which only further renders any findings less relevant.

Third, one of the biggest issues in this study is that ID8 cells are not normal ovarian surface epithelial cells but instead are cells intended to be a model of *ovarian cancer*. This means that the authors did not examine or test talc effects on normal ovarian cells at all. Instead, they examined the effects of talc on already-malignant ovarian cells. In any event, ID8 cells are not even a good model of ovarian cancer, as they are *TP53* wild-type (normal, non-mutated gene) and are derived from the ovarian *surface* whereas most high-grade serous ovarian cancers (the most common type of ovarian cancer) are thought to arise from the fallopian tube epithelium instead. More fundamentally, it is not clear how studying the effects of talc on tumor cells (and irrelevant ones at that) yields any insight into how normal cells become tumor cells.

[82] Mandarino A, Gregory DJ, McGuire CC, Leblanc BW, Witt H, Rivera LM, Godleski JJ, Fedulov AV. *The effect of talc particles on phagocytes in co-culture with ovarian cancer cells.* Environmental Research. 2020 Jan 1;180:108676.

Fourth, the authors examine the effects of these agents on gene expression in the macrophage cell lines using a gene panel relevant to cancer cells not genes relevant to macrophages. As such, any discussion of the potential relevance of these genes for ovarian carcinogenesis is off point. Moreover, the effects on gene expression are modest and inconsistent between the lines examined.

Finally, the authors do appear to show that talc in combination with E2 (both at irrelevantly high levels) led to a 10% or 20% increase in the number of tumor cells as compared to the control. Such a difference is unlikely to be clinically relevant. Notably, when the authors used more appropriate and lower levels of E2, there was no effect of talc on tumor cell survival. In any event, even if we were to take these experiments at face value, there is no reason to believe that macrophages play a major, determinative role in ovarian tumor surveillance.

Overall, this paper does not provide any significant new insight into a potential role for talc in ovarian carcinogenesis.

2. Emi T, Rivera LM, Tripathi VC, Yano N, Ragavendran A, Wallace J, Fedulov AV. Transcriptomic and epigenomic effects of insoluble particles on J774 macrophages. Epigenetics. 2021 Oct 3;16(10):1053-70

This study is an extension of Mandarino (see above) performed by the same senior and corresponding author (A.V. Fedulov), in which the authors claim to "show that talc particles, especially in the context of increased estrogen (E) levels, impair the tumoricidal function of [macrophages] allowing more ovarian cancer cells in a co-culture."[83]

In essence, the investigators employ a single murine (rodent) cell line (J774) that was cultured in plastic petri dishes and treated with one dose of 17-β estradiol (E) or ethanol as a vehicle control, followed by treatment 24 hours later with either one dose of talc (T) or one dose of titanium dioxide (Ti).

The authors reported the effects of T or Ti treatment on global gene expression ("transcriptomic effects") by analyzing genome-wide perturbations in RNA levels and by analyzing the effects on global DNA methylation. Following this analysis, the investigators specifically examined a subset of genes that were methylated.

All tested combinations of T, Ti and E caused multiple and different changes in gene expression compared to no treatment. Further, the number of genes affected by exposure was greater for T conditions compared to Ti conditions. Biological pathway analyses suggests T affected genes (per expression levels) involved in pathways of: 1) cell division/proliferation, 2) macrophage phagocytosis, 3) immune response signaling pathways, 4) MHC class I presentation, 5) oxidative stress-induced signaling, 6) estrogen signaling, 7) apoptosis, and 8) epigenetic regulation.

The authors also reported experimental findings on epigenomics showing some gene methylation profiles were altered by T and Ti (alone or in combination with E). However, the methylation

[83] Emi T, Rivera LM, Tripathi VC, Yano N, Ragavendran A, Wallace J, Fedulov AV. Transcriptomic and epigenomic effects of insoluble particles on J774 macrophages. Epigenetics. 2021 Oct 3;16(10):1053-70, 1053 ("Emi et al. 2021").

effects were largely ***not*** associated with the regions where the "transcription change[s]" were observed.[84] These findings led them to conclude that the data do not "suggest a strong potential for mechanistic involvement of the [differentially methylated loci] we identified with the transcriptional changes we observe at the moment."[85]

The final conclusions of the Discussion section state that, "we postulate that the "reshuffle" of epigenetic machinery induced by the particles may be responsible for downstream malfunctioning of the exposed macrophages we found: the reduced tumoricidal function induced by talc and the enhanced pro-inflammatory responses induced by TiO_2. Overall, our study has led to this 'two-hit' hypothesis that merits further testing."[86]

The major conclusion of the data presented in this study is that the investigators have developed a "hypothesis that merits further testing."[87] As such, it does not provide the missing biological plausibility link in plaintiffs' experts' theories. Moreover, there are numerous flaws in the study rationale and design that undermine any use of this study to explain the hypothesized carcinogenicity of talc. Following are the most notable errors:

a) There is no explanation, stated or implied, as to how observed changes in gene expression and/or gene methylation in a macrophage cell line, derived from a mouse with lymphatic cancer, would be relevant to the transformation of normal human ovarian epithelial cells to malignant ovarian epithelial cells.

b) After having chosen to study a macrophage in this context, the rationale for use of a macrophage cell line obtained from a mouse with a completely distinct type of cancer (malignant lymphoma) is unclear. Immune cells from mice with a completely different kind of cancer are too far from normal human macrophages to render this study relevant even if one accepts the notion that this study or the Mandarino study relate to ovarian carcinogenesis.

c) The investigators examined only one dose of the substances under study (T, Ti, E) at only one time point (24 hours), which was very shortly after exposure of the cells to the xenobiotic agents studied. It is expected that such a cellular insult with any particle or chemical, no matter how inert, would result in rapid changes in gene expression after such an exposure.

d) Changes in the transcriptome and epigenome of the murine macrophage are observed after exposure to both T and Ti, and in some cases these changes overlap. This is to be expected (as above), but it is unclear why the authors would only suggest T (talc) is a carcinogenic agent not Ti (TiO_2).

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84 *Id.* at 1062.

85 *Id.* at 1068.

86 *Id.* (endnotes omitted).

87 *Id.*

e) The use of estradiol in combination with T and Ti is of questionable scientific and clinical foundation; the great majority of epithelial ovarian carcinomas occur in women well past menopause (i.e., average age of 63).

f) As stated by the authors, there is no relationship between induced changes in the transcriptome and changes found in the epigenome, rendering this entire line of scientific inquiry moot. To the extent talc caused epigenetic changes in macrophages, these changes were unrelated to the observed changes in gene expression and subsequent pathway analyses. Because the sets of observations did not pertain to the same areas, these results strongly suggest these induced changes are random and unrelated to carcinogenesis, even if the study design were relevant to ovarian cancer.

For these reasons, this study by Emi et al. provides neither a mechanistic explanation for the preceding study by Mandarino specifically, nor a mechanistic explanation for a putative link between talc exposure and ovarian carcinogenesis generally.

I am aware of two articles recently published online ahead of print. They were obviously not included in plaintiffs' experts' reports, since they were not available at the time those reports were prepared. Nevertheless, I address them briefly here.

3. O'Brien K, Wentzensen N, Ogunsina K, Weinberg C, D'Aloisio A, Edwards J, Sandler D. Intimate care products and incidence of hormone-related cancers: a quantitative bias analysis. Journal of Clinical Oncology. 2024 May 15;epub ahead of print

Although this paper primarily involves epidemiologic data (or more precisely, imputed data) that will presumably be addressed by other experts, I write briefly to address a few points. The authors expressly disclaim any causal conclusion, stating that "[t]hese results do not establish causality and do not implicate any specific cancer-inducing agent."[88] The article does mention mechanistic theories in passing, contending that "[s]ome talc may have been contaminated with asbestos or other potentially harmful chemicals such as phthalates or parabens. Chronic irritation of the ovaries or fallopian tubes from talc or talc-like products could also potentially contribute to carcinogenesis."[89] But the article notes that the authors cannot "pinpoint a specific cause or mechanism." I agree that any mechanistic theories remain—at best—speculative hypotheses for the reasons articulated elsewhere in this report.

[88] O'Brien K, Wentzensen N, Ogusina K, Weinberg C, D'Aloisio A, Edwards J, Sandler D. *Intimate care products and the evidence of hormone-related cancers: a quantitative bias analysis.* Journal of Clinical Oncology. 2024 May; epub ahead of print.

[89] Elsewhere the paper reiterates similar theories: talc may be contaminated with asbestos and it "could plausibly promote carcinogenesis through mechanisms other than direct contact with asbestos, including exposure to other chemicals, or irritation and inflammation of the reproductive tract."

4. Saed G. Is there a link between talcum powder, oxidative stress, and ovarian cancer risk? Expert Review of Anticancer Therapy. 2024 May 8; epub ahead of print

In his recent review article, Dr. Saed claims to present "unequivocal evidence to show that talc is not biologically inert as it induced molecular changes that mimic the hallmarks of cancer."[90] That claim is based primarily on a summary of his own prior work. Indeed, every single mechanistic study highlighted as "of considerable interest" comes from Dr. Saed's own lab, and the review specifically highlights Harper, et al. (2023) as the first (and apparently still only) "evidence of cellular transformation." As discussed above, the work from Dr. Saed's lab is of exceedingly poor quality. Moreover, when the review article summarizes the results of these studies, they remain at odds with the results actually recorded in Dr. Saed's lab notebook.

IV. TALC IS NOT A RECOGNIZED CARCINOGEN

The conclusions of plaintiffs' experts with respect to biological plausibility are also directly contradicted by established science showing that talc is not carcinogenic. Moreover, studies in vitro comparing exposures of talc to exposures to a known carcinogen, asbestos, have shown that talc is not mutagenic. Several studies conducted under the direction of Dr. Brooke T. Mossman investigated the effects on human cells of different types of asbestos as compared to certain control substances, including talc. Shukla 2009[91] studied the effects of crocidolite asbestos, talc, titanium dioxide, and glass beads in human pleural mesothelial and ovarian epithelial cells. The mesothelial and epithelial cells exposed to talc (as well as the other control substances, titanium dioxide and glass beads) did not undergo gene expression changes consistent with carcinogenesis. In Hillegass 2010,[92] this same group of researchers used a purely statistical approach to assess the data produced in Shukla 2009. The results of the Hillegass 2010 study showed that talc, like glass beads and titanium dioxide, is an inert substance that does not cause gene expression changes consistent with any potential pathogenicity. In addition to testing the cosmetic talc found in commercially available baby powder, as they did in Shukla 2009 and Hillegass 2010, Dr. Mossman and her team have also tested fibrous talc and asbestos in studies in vitro to determine whether fibrous talc caused similar biological responses in cells as those caused by asbestos. In Wylie 1997,[93] Dr. Mossman and her fellow researchers found that fibrous talc compared to asbestos did not produce the same or any increase in colony forming efficiency (a measure of cellular transformation) in tracheal epithelial cells, or cytotoxicity equivalent to asbestos in either tracheal epithelial cells or

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[90] Saed G. Is there a link between talcum powder, oxidative stress, and ovarian cancer risk? Expert Review of Anticancer Therapy. 2024 May; epub ahead of pint.

[91] Shukla A, MacPherson MB, Hillegass J, Ramos-Nino ME, Alexeeva V, Vacek PM, Bond JP, Pass HI, Steele C, Mossman BT. *Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity*. American Journal of Respiratory Cell and Molecular Biology. 2009 Jul;41(1):114-23.

[92] Hillegass JM, Shukla A, MacPherson MB, Bond JP, Steele C, Mossman BT. *Utilization of gene profiling and proteomics to determine mineral pathogenicity in a human mesothelial cell line (LP9/TERT-1)*. Journal of Toxicology and Environmental Health, Part A. 2010 Feb 19;73(5-6):423-36.

[93] Wylie AG, Skinner HC, Marsh J, Snyder H, Garzione C, Hodkinson D, Winters R, Mossman BT. *Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells*. Toxicology and Applied Pharmacology. 1997 Nov 1;147(1):143-50.

pleural mesothelial cells. These data implicate the importance of mineral type, rather than fiber length *per se*, in determining pathogenicity of mineral dusts.[94]

In sum, the scientific literature shows that talc—both the cosmetic talc found in baby powder and so-called "fibrous talc"—is not carcinogenic.

V. DR. SHAWN LEVY'S EXPERT REPORT

My review of Dr. Levy's CV left me troubled to say the least. Of the 221 papers listed on his CV, he is first or last author on only 14 (6.3%) of these papers. This extremely low first or last-authorship rate strongly suggests that his role on the vast majority of his published work is supportive in nature, rather than in the design, execution, interpretation and writing of the papers. Further, *none* of the publications in which Dr. Levy is listed as a coauthor involve ovarian cancer.

Most disturbing, *Dr. Levy does not appear as an author at all on 11 papers listed on his CV.* Omission of his name on these papers cannot be attributed to mistakes in the preparation of his CV, as I confirmed the author lists for these papers on PubMed. This is a violation of ethical conduct in the biomedical profession.

Turning to the substance of his report, Dr. Levy correctly outlines the critical role of genetic mutations, both inherited and acquired (somatic), as the driving force of cancer development. However, in discussing acquired or somatic mutations (which constitute the great majority of mutations in all cancers), he incorrectly implies that these mutations all or mostly result from exposures to carcinogens. That is incorrect. It is well documented and widely accepted that most somatic mutations typically arise purely as a result of chance during the process of cell division and replication of the cellular genome over the course of a lifetime (approximately 3.3 billion base pairs per cell, and trillions of cells in the human body having arisen from one). While DNA can sometimes be repaired, these mistakes may persist, ultimately leading to the accumulation of mutations that are sufficient to create a malignancy in one or another organ. The theoretical basis for this model of cancer development is described by Tomasetti and Vogelstein.[95]

The most outrageous claim in Dr. Levy's report is his unsupported suggestion that having an inherited mutation in a gene such as *BRCA1* affects the degree to which an exposure increases risk for developing ovarian cancer. For example, Dr. Levy writes that, "inherited gene mutation[s] could increase susceptibility to cancer when someone is exposed to a specific cancer-causing substance."[96] He specifically believes this to be true for "chemical and other environmental agents, such as talcum powder."[97] These statements are entirely speculative. Dr. Levy provides no

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[94] It is also worth noting that the studies in vitro supposedly addressing talc and its mutagenic potential have not touched on uterine cancer. For example, there do not appear to be any talc studies like those done by Dr. Saed conducted on endometrial cells. Nor have I seen mechanistic cell studies focused specifically on borderline ovarian tumors as a subset of epithelial ovarian neoplasms.

[95] Tomasetti C, Vogelstein B. *Variation in cancer risk among tissues can be explained by the number of stem cell divisions*. Science. 2015 Jan 2;347(6217):78-81.

[96] Am. Levy Rep. at 5.

[97] *Id.*

citations or data that potential carcinogens increase the penetrance (lifetime risk) of inherited mutations in terms of cancer risk.

As part of this recurring false narrative, when referring to *BRCA1/2*, Dr. Levy writes that, "[t]hese mutations make a person more susceptible to developing cancer when exposed to a carcinogen (Park, 2018; Vitonis, 2011; Wu, 2015)."[98] Not a single one of the three citations provided supports the preceding statement. When briefly referencing Lynch syndrome, another genetic disorder that increases risk of ovarian cancer, Dr. Levy again writes "the risk of cancer will increase when exposed to a carcinogen."[99] As I explained above, there is no evidence that carcinogen exposure increases the penetrance of any gene mutations related to ovarian cancer, including those that cause Lynch syndrome.

It is critical to recognize that plaintiffs' theory in this litigation rests on the supposition that genital talc use and inflammation are instrumental to ovarian cancer ***initiation***. This means studies about how talc use (or inflammation) affects the behavior of ovarian cancer cells that have already been transformed do not advance the ball on plaintiffs' core mechanistic theory. Plaintiffs' experts (especially Dr. Levy) repeatedly cite and comment on studies and analyses that examine what happens to already-malignant ovarian cancer cells. Once placed in proper context, these citations are virtually meaningless for the question at hand. The conflation of ovarian cancer pathogenesis (initiation and causation) with ovarian cancer behavior once the malignancy exists is a repetitive flaw in the reports of plaintiffs' experts.

This is true for studies on inflammation and studies on talc use. For instance, Dr. Levy cites a study examining the role of inflammation and wound healing, writing that, "[r]ecent studies have shown a link between inflammation associated with wound healing and ovarian cancer cell seeding (Jia, Nagaoka et al. 2018)."[100] This statement is correct and supported by the citation. However, the Jia study begins with mouse ovarian cancer cells or already-malignant ovarian cancer cells. Like Emi and Mandarino above, it does not tell us anything about carcinogenesis.

When discussing inflammation generally, Dr. Levy begins by citing the work of Rudolf Virchow in 1863, on "[t]he functional relationship between cancer and inflammation" and a similar piece by Balkwill and Mantovani.[101] As Balkwill stated, all they have hypothesized is that if genetic damage is the "match that lights the fire" of cancer, some types of inflammation may provide the "fuel that feeds the flames."[102] Again, this refers to inflammatory events that happen ***after*** cancer has already begun.

Later in his report, Dr. Levy cites additional epidemiologic observations on inflammation, with focus on a study by Brieger et al., in which talc use is purported to result in worse outcomes from

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98 *Id.* at 8.

99 *Id.* at 9.

100 *Id.* at 10.

101 *Id.* at 10-11; *see* Balkwill F, Mantovani A. *Inflammation and cancer: back to Virchow?*. The Lancet. 2001 Feb 17;357(9255):539-45.

102 Am. Levy Rep. at 11.

ovarian cancer.[103] These data are irrelevant to the hypothesis that talc is carcinogenic, since the women studied have already been diagnosed with ovarian cancer.

Dr. Levy also writes that "[t]he chronic inflammation model of carcinogenesis proposes that chronic exposures to external or endogenous triggers of immunity . . . cause ovarian cancer."[104] He believes that talcum powder causes chronic inflammation that in turn causes ovarian cancer, but this theory is based on the flawed work of Dr. Saed on ROS and cytokine production (Saed, Diamond and Fletcher 2017).[105] As I noted in my previous report (see above), this work of Dr. Saed and colleagues has been thoroughly debunked and is far too methodologically unsound to support the chronic inflammation theory.

Dr. Levy also posits that evidence regarding "incessant ovulation" as a risk factor for ovarian cancer supports the inflammation theory.[106] While this epidemiologic association is widely accepted in the ovarian cancer research community, the *mechanism* for this relationship remains elusive.[107] Dr. Levy states that, "[m]any cancers arise from sites with chronic irritation, infection, or inflammation. Cancer cells persist in a pro-oxidant state with excess production and ROS generation that allows for tumor initiation, promotion, and progression."[108] There is a temporal problem here. It is not clear whether the irritation, infection, or inflammation (and ROS) result from the cancer cells or precede the transformation to cancer.[109] In short, there is no evidence for this mechanistic paradigm in ovarian cancer.

Dr. Levy also cites an in vitro study by Buz'Zard and Lau, who "reported an increase in ROS generation, increased cell proliferation, and neoplastic transformation (conversion into cancerous cells) in human ovarian cells treated with talcum powder."[110] The data in this study actually showed that talcum powder *reduced* the generation of ROS (reactive oxygen species) and ***decreased*** cell proliferation. Furthermore, neoplastic transformation of the immortalized cells under study into cancer cells was *not* observed in this study.

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[103] *See id.* at 16; *see* Brieger KK, Phung MT, Mukherjee B, Bakulski KM, Anton-Culver H, Bandera EV, Bowtell DD, Cramer DW, DeFazio A, Doherty JA, Fereday S. *High prediagnosis inflammation-related risk score associated with decreased ovarian cancer survival*. Cancer Epidemiology, Biomarkers & Prevention. 2022 Feb 1;31(2):443-52.

[104] Am. Levy Rep. at 12.

[105] *See id.*

[106] *Id.*

[107] *See* Vercellini P, Crosignani P, Somigliana E, Vigano P, Buggio L, Bolis G, Fedele L. *The 'incessant menstruation' hypothesis: a mechanistic ovarian cancer model with implications for prevention*. Human Reproduction. 2011 Sep 1;26(9):2262-73.

[108] Am. Levy Rep. at 13.

[109] *See* Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, Makrigiannakis A, Gray H, Schlienger K, Liebman MN, Rubin SC. *Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer*. New England Journal of Medicine. 2003 Jan 16;348(3):203-13.

[110] *Id.* at 15; *see* Buz'Zard & Lau 2007.

Dr. Levy also states that, "[a]dditional studies have also shown the effects of talc on the immune response," referring to two animal studies: (1) Hamilton et al. and (2) Keskin et al.[111] In both studies, large amounts of talc were injected into rat ovaries or the rat vagina unlike the exposures at issue in this litigation. More importantly, no ovarian tumors were observed in either study. Dr. Levy's assertion that foreign body reactions and infections are apparently evidence of an immune response is not surprising but overlooks the lack of tumor formation in both studies.

Given the many errors in his report, it is not surprising that the majority of Dr. Levy's conclusions are false, misleading, or both. Specifically:

1. "*Inflammation has been shown to play a vital role in epithelial ovarian cancer.*"[112] This statement is false. There is no evidence that inflammation is involved in the initiation or progression of ovarian cancer carcinogenesis.

2. "*Talcum powder products cause chronic inflammation.*"[113] Other than in the context of medical pleurodesis, wherein very large amounts of talc are used to close the pleural space through the generation of fibrosis, a type of acute inflammation, this statement is otherwise false. There is no evidence that talcum powder causes chronic inflammation.

3. "*Talcum powder product-induced inflammation causes damage to the DNA, genetic mutation, genomic instability, and cell transformation.*"[114] This statement is false. There is no credible evidence that talcum powder causes any type of DNA damage or malignant transformation of cells.

4. "*The properties and constituents of talcum powder products act as inflammatory agents and the role of inflammation in triggering oxidative stress, activating cytokines, cell proliferation, DNA damage, and genetic mutations (such as SNVs) provide a biologically plausible mechanism for the carcinogenicity of talcum powder products.*"[115] This statement is false. There is no evidence that talcum powder acts as an inflammatory agent, and the occurrence of the ensuing sequela listed are not supported by the published literature, irrespective of the presence of inflammation. Thus, there is no biological plausibility for the claimed carcinogenicity of talcum powder.

5. "*Internalization of asbestiform fibers (including asbestos and fibrous talc) causes DNA damage, which provides a biologically plausible mechanism for the carcinogenicity of*

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111 *Id.*; *see* Hamilton TC, Fox HC, Buckley CH, Henderson WJ, Griffiths K. *Effects of talc on the rat ovary*. British Journal of Experimental Pathology. 1984 Feb;65(1):101; Keskın N, Teksen YA, Ongun EG, Özay Y, Saygılı H. *Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study*. Archives of Gynecology and Obstetrics. 2009 Dec;280:925-31.

112 Am. Levy Rep. at 24 (emphasis added).

113 *Id.* (emphasis added).

114 *Id.* (emphasis added).

115 *Id.* at 25 (emphasis added).

talcum powder products."[116] This statement is misleading at best. Because there is no evidence that talcum powder causes DNA damage, the above statement is irrelevant to biological plausibility related to talcum powder and ovarian carcinogenesis.

6. "*Women with inherited gene mutations in genes involved in DNA repair, such as BRCA1 or BRCA2, are more as [sic] susceptible to the effect of carcinogens than women without inherited gene mutations.*"[117] This statement is misleading. The *BRCA1/2* proteins are involved in the homologous recombination DNA repair pathway. The "effect of carcinogens" (whatever that may be) on women with inherited mutations in *BRCA1/2*, and defective HR-mediated DNA repair of double-strand breaks, has not been studied, and would in fact be very difficult to study for obvious reasons.

All of my opinions in this report are stated to a reasonable degree of scientific certainty.

VI. SUPPLEMENTAL MATERIALS CONSIDERED

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[116] *Id.* (emphasis added).

[117] *Id.* (emphasis added).

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38. Second Amended Expert of Report of Judith Wolf, MD, dated November 15, 2023.

39. Amended Rule 26 Expert Report of Shawn Levy, PhD, dated November 15, 2023.

40. Expert Report of Michele L. Cote, Ph.D., M.P.H., dated November 15, 2023.

41. Second Amended Expert Report of Anne McTiernan, MD, Ph.D., dated November 15, 2023.

42. Second Amended Expert Report of Laura M. Plunkett, Ph.D., DABT, dated November 15, 2023.

43. Second Amended Expert Report of Rebecca Smith-Bindman, MD, dated November 15, 2023.

44. Supplemental Expert Report of Sonal Singh, MD, MPH, dated November 15, 2023.